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TITLE PAGE

CLINICAL STUDY REPORT NO: 1103873 STUDY INFORMATION

TITLE:	**AVANTI: NON-INTERVENTIONAL POST MARKETING SURVEILLANCE STUDY (NIS) ON BEVACIZUMAB (AVASTIN®) IN COMBINATION WITH PACLITAXEL OR CAPECITABINE (XELODA®) IN PATIENTS WITH METASTATIC BREAST CANCER**
PROTOCOL NUMBER:	ML22452 (Roche Pharma AG) P0158 (iOMEDICO AG)
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CLINICAL STUDY REPORT APPROVAL

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1. SYNOPSIS/ABSTRACT

Title

AVANTI: NON-INTERVENTIONAL POST MARKETING SURVEILLANCE STUDY (NIS) ON BEVACIZUMAB (AVASTIN®) IN COMBINATION WITH PACLITAXEL OR CAPECITABINE (XELODA®) IN PATIENTS WITH METASTATIC BREAST CANCER

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Keywords

Metastatic breast cancer ▪ bevacizumab (Avastin®) combination therapy ▪ routine clinical practice ▪ non-interventional study ▪ Germany

Research Question and Objectives

This non-interventional study (NIS) was designed to document data on decision making and selection criteria in patients with human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer treated with first-line bevacizumab (Avastin®) in combination with paclitaxel or capecitabine (Xeloda®) in routine clinical practice in Germany and to capture data on effectiveness and safety as well as patient-reported quality of life (QoL) and treatment satisfaction of these treatment combinations in the total population and in pre-defined subgroups (e.g., the subgroup of patients aged ≥60 years and the subgroup of patients with triple-negative breast cancer (TNBC)).

Study objectives

The primary objectives were as follows:

- Deciding institution and decision criteria for choosing paclitaxel or capecitabine (Xeloda®) as combination partner for bevacizumab (Avastin®)
- The incidence of rare serious adverse events
- The incidence of adverse events of special interest (bevacizumab (Avastin®)-associated hypertension and proteinuria) overall and in subgroups of patients aged <60 years or ≥60 years treated with bevacizumab (Avastin®) in combination with paclitaxel or capecitabine (Xeloda®)

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- The overall and domain-related quality of life (EORTC QLQ-C30) in patients treated with paclitaxel or capecitabine (Xeloda®)-containing regimen during treatment overall and in subgroups according to age (<60 years vs. ≥60 years)

The secondary objectives included:

- Demographic characteristics and medical history of the patient
- Response and time-to-event effectiveness parameters of bevacizumab (Avastin®) in combination with paclitaxel or capecitabine (Xeloda®) overall and in pre-defined clinically relevant subgroups
- Information on diagnostics and therapy management especially focusing on the bevacizumab (Avastin®)-associated adverse events “hypertension” and “proteinuria”
- Safety of bevacizumab (Avastin®)-based therapy in combination with paclitaxel or capecitabine (Xeloda®)
- Safety of bevacizumab (Avastin®)-based therapy in combination with paclitaxel or capecitabine (Xeloda®) in elderly patients (aged ≥60 years) compared to the younger patient population (aged <60 years)
- Patient’s subjective experience of therapy side-effects for paclitaxel or capecitabine (Xeloda®)-containing regimen during treatment overall and in subgroups according to age (<60 years vs. ≥60 years)
- Patient’s satisfaction with bevacizumab (Avastin®)-based therapy
- Physician’s satisfaction with bevacizumab (Avastin®)-based therapy

Study design

This study was a multicenter, non-interventional study conducted in Germany in accordance with section 67 (paragraph 6) of the German Drug Act (AMG), which involved primary data collection.

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Target Population Patients were recruited from 1 November 2009 (first-patient-in) through 30 April 2016 (last-patient-in) in 346 study sites across Germany including oncologists and gynecologists in hospitals and outpatient clinics, and independent oncology practices. Eligible patients were aged ≥18 years, diagnosed with HER2-negative locally advanced, recurrent or metastatic breast cancer and with decision for first-line therapy with bevacizumab (Avastin®) in combination with paclitaxel or capecitabine (Xeloda®) in routine clinical practice. The maximum duration of documentation period per patient was 30 months after enrollment comprising an intense documentation period of bevacizumab (Avastin®) therapy for a maximum of 12 months or until premature discontinuation of bevacizumab (Avastin®) therapy, and a follow-up period for a maximum of 18 months (every 6 months).

Study size

In this study, 2,988 patients were enrolled in 346 study sites, of these, 923 patients were excluded from final data analysis as they did not meet the inclusion criteria.

Studied medicinal product

Avastin® (bevacizumab)

Variables

Primary effectiveness variable

- There was no primary effectiveness variable in this study as all the effectiveness variables were secondary outcome measures.

Secondary effectiveness variables

- Progression-free survival (PFS) defined as the time from first bevacizumab (Avastin®) application to disease progression or death due to any cause, whichever came first.
- Overall survival (OS) defined as the time from first bevacizumab (Avastin®) application to death due to any cause.
- Best response defined as the best documented response under bevacizumab (Avastin®)-based first-line therapy.
- Objective response rate (ORR) defined as the proportion of patients having a complete response (CR) or partial response (PR) as best response.

Safety variables

- Adverse events (AEs) including AEs requiring expedited reporting:

[redacted]

[redacted]

  - AEs related to quality deficiencies
  - AEs related to counterfeits (or suspicion)
  - AEs related to occupational exposure
- AEs of special interest: bevacizumab (Avastin®)-associated hypertension and proteinuria (primary objective)
- Serious AEs (SAEs)
- Causally related (S)AEs (attributable to bevacizumab (Avastin®) / capecitabine (Xeloda®))
- Fatal SAEs (regardless of causality)
- Fatal bevacizumab (Avastin)-related SAEs
- AEs leading to study discontinuation or treatment discontinuation
- Pregnancy

Other variables of interest

- Criteria and deciding institution for choosing paclitaxel or capecitabine (Xeloda®) as combination partner for bevacizumab (Avastin®; primary objective)
- Overall and domain-related quality of life (EORTC QLQ-C30; primary objective)
- Patient's subjective experience of therapy side-effects for paclitaxel or capecitabine (Xeloda®)-containing regimen during treatment overall and in subgroups according to age (<60 years vs. ≥60 years)
- Patient satisfaction with bevacizumab (Avastin®)-based therapy
- Physicians satisfaction with bevacizumab (Avastin®)-based therapy

Data Sources

The electronic data capture system was provided by iOMEDICO AG, i.e. the CRO which supported the study as full-service provider. Data were derived from electronic Case Report Form (eCRF)-entries made by the study sites as part of routine clinical practice. Data were transferred from source documents (i.e., patient's medical records) to the eCRF and subjected to quality checks according to iOMEDICO- and Roche-specific SOPs.

The handling of paper-based questionnaires (EORTC QLQ-C30, patient satisfaction questionnaire, and patient symptoms questionnaire) was organized with the support of iOMEDICO Site Management Organization GmbH. Paper-based patient questionnaires served as source documents.

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Statistical and Epidemiological Methods

Time-to-event endpoints (PFS and OS) were estimated by using the Kaplan-Meier method to present time-to-event data together with number of events and number of censored cases as well as quartiles and corresponding 95% CI.

Differences in PFS/OS data between pre-defined clinically relevant subgroups were assessed by using the log-rank test, i.e., comparison of PFS/OS over all event time points (the whole PFS/OS curve). Hazard ratios between the subgroups were estimated by using multivariable Cox regression together with 95% CI. Efron method was used to control for ties.

Odds ratios for ORR between pre-defined clinically relevant subgroups were estimated by using multivariable logistic regression and are reported accompanied by 95% CI (Wald) and *p*-values (Wald test).

Duration of therapy was estimated by using the Kaplan-Meier method.

Changes from baseline in the quality of life (QoL) scale were evaluated for each timepoint (baseline, week 9, week 15, week 33 and week 54 or premature end of bevacizumab (Avastin®) therapy) by using a paired t-test (two-sided, ALPHA error rate = 5%).

Binomial 95% CI was calculated by using the Agresti-Coull method (evaluation of ORR and TEAEs).

CONSORT Flow Diagram

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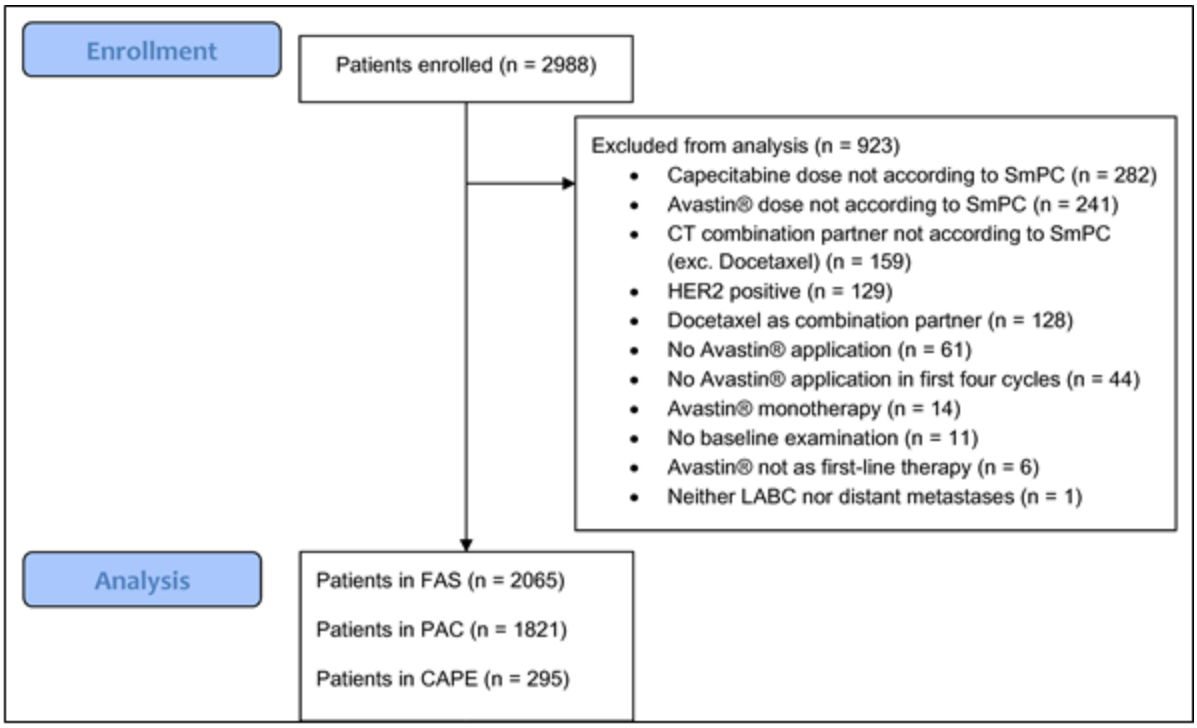

Analysis Populations – Definitions and Further Inclusion / Exclusion Criteria

- Full analysis set (FAS): The FAS comprised all patients who had received at least one dose of bevacizumab (Avastin®) and were eligible according to the DRM protocol. Patients with off-label use of bevacizumab (Avastin®) as per current version of the SmPC were included in the FAS if they had been treated in-label at time of inclusion into the study. Patients with ≥10% deviation of bevacizumab (Avastin®) dosing with regards to current SmPC both in the first and second cycle were excluded from the FAS. If the bevacizumab (Avastin®) dosing was in accordance with current SmPC in one of the two first cycles the patient was included in the FAS. Patients having received a capecitabine (Xeloda®) dose of <800 mg/m^2 or >5600 mg/m^2 in the first cycle were excluded from the FAS.

- Capecitabine (Xeloda®, CAPE): The CAPE analysis population comprised all patients who qualified for the FAS and had received at least one dose of capecitabine (Xeloda®) in combination with bevacizumab (Avastin®).

- Paclitaxel (PAC): The PAC analysis population comprised all patients who qualified for the FAS and had received at least one dose of paclitaxel in combination with bevacizumab (Avastin®).

In case of therapy switch from paclitaxel + bevacizumab (Avastin®) to capecitabine (Xeloda®) + bevacizumab (Avastin®) (or vice versa), patients were assigned to both the PAC population and the CAPE population (n=51).

Pre-defined clinically relevant subgroups included in the final analysis (effectiveness analysis)

Subgroup	Specification of subgroup analyses
Hypertension	Hypertensive patients vs. normotensive patients (at baseline)
Triple-negative breast cancer (TNBC)	TNBC patients vs. non-TNBC patients vs. patients with unknown status[5]
Age[1]	Patients aged <60 years vs. patients aged ≥60 years
Liver metastases	Patients with liver metastases only vs. all other patients[6]
Number of metastases	Patients with <3 sites vs. patients with ≥3 sites
Prior anthracycline/taxane therapy (AC/TX)[2]	Patients with prior AC/TX vs. patients without prior AC/TX
Prior endocrine therapy (ET)[3]	Patients with prior ET vs. patients without prior ET
Urgency to treat[4]	Patients with high urgency to treat vs. all other patients

AC = Anthracycline; ET = Endocrine therapy; TNBC = Triple-negative breast cancer; TX = Taxane
[1]The age subgroups were additionally included in certain safety analyses (TEAEs of special interest: bevacizumab (Avastin®)-associated hypertension and proteinuria).
[2]Prior AC/TX refers to anthracycline or taxane treatment in the (neo-)adjuvant setting.
[3]Prior ET refers to any prior endocrine treatment in the metastatic setting before combined treatment with bevacizumab (Avastin®) and chemotherapy.
[4]Urgency to treat: defined as patients fulfilling at least three of the following criteria: ≥3 metastatic sites, liver metastasis, prior ([neo-]adjuvant) anthracycline/taxane therapy, or TNBC.
[5]Patients with unknown status were not included in the final SAP v1.0 but requested by Roche to be included in the final analysis.
[6]Other: patients with other metastatic sites or locally advanced or recurrent disease.

Results

All the study objectives were met and evaluated.

Effectiveness was additionally analyzed in the pre-defined clinically relevant subgroups. In the synopsis, only the subgroups “Hypertension”, “TNBC” and “Age” are included as potential differences within these subgroups are of special interest:

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Subgroup categories	FAS (N=2065)	PAC (N=1821)	CAPE (N=295)
Hypertensive[1] [n, %]	707 (34.2%)	623 (34.2%)	107 (36.3%)
Normotensive[1] [n, %]	1358 (65.8%)	1198 (65.8%)	188 (63.7%)
TNBC[2] [n, %]	425 (20.6%)	363 (19.9%)	74 (25.1%)
Non-TNBC[2]	1513 (73.3%)	1346 (73.9%)	201 (68.1%)
Unknown status[2]	127 (6.2%)	112 (6.2%)	20 (6.8%)
<60 years [n, %]	1046 (50.7%)	930 (51.1%)	137 (46.4%)
≥60 years [n, %]	1019 (49.3%)	891 (48.9%)	158 (53.6%)

CAPE = Capecitabine analysis population; FAS = Full analysis set; N/n = Number; PAC = Paclitaxel analysis population; TNBC = Triple-negative breast cancer
[1]At baseline.
[2]In the description of the results, the subgroups of TNBC and non-TNBC will be compared.

PATIENT CHARACTERISTICS AT BASELINE

In the total population (FAS), the median age (min – max) at start of therapy was 59.8 years (23.9 – 86.7 years); 1019 (49.3%) patients were aged ≥60 years. TNBC was reported in 425 (20.6%) patients. Most patients were reported with invasive ductal carcinoma (n=1490; 72.2%) and tumors of histological grade 2 (n=1033; 50.0%) or grade 3 (n=769; 37.2%). In total, 609 (29.5%) patients were documented with metastases (M1) at initial diagnosis. Most patients were documented with <3 metastatic sites (n=1651; 80.0%); 220 (10.7%) patients were reported with only liver metastases.

There was no major difference in the median age (min – max) at start of therapy between the PAC (59.7 years (23.9 – 86.4 years)) and CAPE (61.2 years (28.5 – 86.7 years)) populations, while the proportion of patients aged ≥60 years was slightly higher in the CAPE population (n=158; 53.6%) as compared to the PAC population (n=891; 48.9%). The proportion of patients with TNBC was higher in the CAPE population (n=74; 25.1%) vs. the PAC population (n=363; 19.9%). Most patients both in the PAC (n=1308; 71.8%) and CAPE (n=221; 74.9%) were documented with invasive ductal carcinoma. The proportion of patients with tumors of histological grade 2 was slightly higher in the PAC population (n=921; 50.6%) as compared to the CAPE population (n=139; 47,1%), whereas the relative frequency of tumors of histological grade 3 was higher in the CAPE population (n=126; 42.7%) vs. the PAC population (n=664; 36.5%). In the PAC population, tumors of undefined histological grade 4 were reported in 2 patients (0.1%).

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The proportion of patients reported with metastases (M1) at initial diagnosis was markedly higher in the PAC population (n=570; 31.3%) than in the CAPE population (n=48; 16.3%). Most patients both in the PAC (n=1441; 79.1%) and CAPE (n=248; 84.1%) populations were reported with <3 metastatic sites. The proportion of patients with metastases localized to the liver only was similar between the PAC (n=196; 10.8%) and CAPE (n=34; 11.5%) populations.

THERAPY DECISION – DECIDING INSTITUTION AND CRITERIA (PRIMARY OBJECTIVE)

In the FAS population, therapy decision was mainly taken by the tumor board (n=1294; 62.7%) or office-based oncologist (n=338; 16.4%). The proportion of patients for whom the therapy decision had been taken by the tumor board was slightly higher in the PAC population (n=1149; 63.1%) as compared to the CAPE population (n=178; 60.3%), while the proportion of patients for whom the therapy decision had been taken by office-based oncologist was markedly higher in the CAPE population (n=71; 24.1%) as compared to the PAC population (n=276; 15.2%).

The two major (>50% of patients) reasons for choice of therapy in the FAS population were “efficacy of therapy” (n=1352; 65.5%) and “guideline” (n=1173; 56.8%). The proportion of patients for whom “efficacy of therapy” (PAC: n=1214; 66.7% vs. CAPE: n=172; 58.3%) and “guideline” (PAC: n=1056; 58.0% vs. CAPE: n=147; 49.8%) were the reported reasons for choice of therapy were higher in the PAC population as compared to the CAPE population.

DURATION OF THERAPY

The Kaplan-Meier estimated median (95% CI) duration of therapy in the FAS population was 6.3 months (6.0 – 6.8 months); the median duration of bevacizumab (Avastin®) therapy was 6.0 months (5.6 – 6.3 months) and the median duration of chemotherapy was 4.2 months (4.0 – 4.2 months). The median duration of bevacizumab (Avastin®) therapy was slightly longer in the PAC population (6.2 months (5.8 – 6.7 months)) as compared to the CAPE population (5.6 months (5.1 – 6.6 months)), while the median duration of chemotherapy was 4.2 months in both populations.

EFFECTIVENESS

Best Response and Objective Response Rate

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Total Analysis Populations

Overall, 121 (5.9%) patients in the FAS population were reported with a CR and 883 (42.8%) patients with a PR, resulting in an ORR (95% CI) at 48.6% (46.5% - 50.8%). The ORR was markedly higher in the PAC population (50.6% (48.3% - 52.9%)) as compared to the CAPE population (39.0% (33.6% - 44.7%)).

Subgroups: Hypertensive Patients vs. Normotensive Patients

In the FAS population, there was no major difference in the proportion of patients reported with a CR or PR between the subgroups of hypertensive patients (CR: n=42; 5.9%; PR: n=312; 44.1%) and normotensive patients (CR: n=79; 5.8%; PR: n=571; 42.0%) with a slightly higher ORR in the subgroup of hypertensive patients (50.1% (46.4% - 53.7%)) as compared to the subgroup of normotensive patients (47.9% (45.2% - 50.5%)).
In the PAC population, the ORR was similar in the subgroups of hypertensive patients (51.0% (47.1% - 55.0%)) and normotensive patients (50.4% (47.6% - 53.2%)), whereas in the CAPE population, the ORR was markedly higher in the subgroup of hypertensive patients (48.6% (39.3% - 58.0%)) as compared to the subgroup of normotensive patients (33.5% (27.1% - 40.5%)).

Subgroups: TNBC Patients vs. Non-TNBC Patients

The proportion of patients in the FAS population reported with a CR was slightly higher in the subgroup of TNBC patients (n=35; 8.2%) as compared to the subgroup of non-TNBC patients (n=76; 5.0%), while the proportion of patients with a PR was markedly higher in the subgroup of non-TNBC patients (n=674; 44.5%) vs. the subgroup of TNBC patients (n=156; 36.7%), resulting in a lower ORR in the latter subgroup (44.9% (40.3% - 49.7%) vs. 49.6% (47.1% - 52.1%)).
In the PAC population, the ORR was slightly lower in the subgroup of TNBC patients (48.5% (43.4% - 53.6%)) as compared to the subgroup of non-TNBC patients (51.0% (48.4% - 53.7%)), while in the CAPE population, the ORR was markedly higher in the subgroup of non-TNBC patients (41.8% (35.2% - 48.7%)) as compared to the subgroup of TNBC patients (32.4% (22.8% - 43.8%)).

Subgroups: Patients Aged <60 Years vs. Patients Aged ≥60 Years

The proportion of patients in the FAS population reported with a CR or PR was higher in the subgroup of patients aged <60 years (CR: n=69; 6.6%; PR: n=473; 45.2%) as

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compared to the subgroup of patients aged ≥60 years (CR: n=52; 5.1%; PR: n=410; 40.2%), resulting in a lower ORR in the latter subgroup (45.3% (42.3% - 48.4%) vs. 51.8% (48.8% - 54.8%)).

The same pattern was seen in the PAC population with highest ORR observed in the subgroup of patients aged <60 years (54.2% (51.0% - 57.4%)) as compared to the subgroup of patients aged ≥60 years (46.9% (43.7% - 50.2%)), whereas in the CAPE population, the ORR was similar in both age subgroups (<60 years: 38.0% (30.3% - 46.3%) vs. ≥60 years: 39.9% (32.6% - 47.7%)).

Progression-Free Survival

Total Analysis Populations

Overall, 1085 (52.5%) patients in the FAS population were reported having experienced an event (PD or death). The median (95% CI) PFS was 12.6 months (11.9 – 13.2 months). The proportion of patients with an event was markedly higher in the CAPE population (n=191; 64.7%) as compared to the PAC population (n=932; 51.2%). The median PFS was longer in the PAC population (12.8 months (12.3 – 13.5 months)) than in the CAPE population (10.5 months (9.0 – 11.7 months)).

Subgroups: Hypertensive Patients vs. Normotensive Patients

In the FAS population, the median PFS was slightly longer in the subgroup of hypertensive patients (13.6 months (12.5 – 15.4 months)) as compared to the subgroup of normotensive patients (11.9 months (11.3 – 12.8 months)).

The observation of a slightly longer median PFS in the subgroup of hypertensive patients as compared to the subgroup of normotensive patients was made both in the PAC population (13.8 months (12.6 – 15.6 months) vs. 12.5 months (11.6 – 13.2 months)) and the CAPE population (11.8 months (10.0 – 16.0 months) vs. 9.6 months (8.5 – 11.0 months)).

Subgroups: TNBC Patients vs. Non-TNBC Patients

In the FAS population, the median PFS was longer in the subgroup of non-TNBC patients (12.9 months (12.1 – 13.8 months)) as compared to the subgroup of TNBC patients (10.3 months (9.2 – 11.6 months)).

The observation of a longer median PFS in the subgroup of non-TNBC patients as compared to the subgroup of TNBC patients was made both in the PAC population (13.3 months (12.4 – 14.4 months) vs. 11.0 months (9.9 – 12.6 months)) and the CAPE population (11.3 months (9.7 – 13.0 months) vs. 8.5 months (6.5 – 9.8 months)).

Subgroups: Patients Aged <60 Years vs. Patients Aged ≥60 Years

In the FAS population, the median PFS was similar in both age subgroups (<60 years: 12.3 months (11.5 – 13.1 months) vs. ≥60 years: 12.8 months (11.9 – 14.1 months)).
In the PAC population, the median PFS was identical in the subgroups of patients aged <60 years (12.8 months (11.8 – 13.8 months)) and ≥60 years (12.8 months (11.9 – 14.3 months)), while in the CAPE population, the median PFS was longer in the subgroup of patients aged ≥60 years (12.4 months (10.2 – 15.1 months)) as compared to the subgroup of patients aged <60 years (8.7 months (7.3 – 10.2 months)).

Overall Survival

Total Analysis Populations

Overall, 982 (47.6%) patients in the FAS population were documented with death with a date of death (event). The median (95% CI) OS was 23.9 months (22.2 – 25.1 months). The proportion of patients documented with an event was higher in the CAPE population (n=163; 55.3%) as compared to the PAC population (n=847; 46.5%). The median OS was longer in the PAC population (24.5 months (22.8 – 25.8 months)) as compared to the CAPE population (20.4 months (17.2 – 23.8 months)).

Subgroups: Hypertensive Patients vs. Normotensive Patients

In the FAS population, the median OS was longer in the subgroup of hypertensive patients as compared to the subgroup of normotensive patients (25.1 months (22.6 – 27.8 months) vs. 23.2 months (21.4 – 25.0 months)).
The observation of a longer median OS in the subgroup of hypertensive patients as compared to the subgroup of normotensive patients was made both in the PAC population (25.1 months (22.5 – 28.6 months) vs. 24.1 months (22.1 – 26.0 months)) and the CAPE population (24.7 months (21.3 – 29.9 months) vs. 17.2 months (14.8 – 19.8 months)).

Subgroups: TNBC Patients vs. Non-TNBC Patients

In the FAS population, the median OS was markedly longer in the subgroup of non-TNBC patients as compared to the subgroup of TNBC patients (25.2 months (23.8 – 27.1 months) vs. 16.8 months (15.3 – 19.3 months)).

The observation of a markedly longer median OS in the subgroup of non-TNBC patients as compared to the subgroup of TNBC patients was made both in the PAC population (25.5 months (24.0 – 28.5 months) vs. 17.8 months (15.8 – 20.3 months)) and the CAPE population (23.0 months (19.3 – 27.1 months) vs. 14.0 months (9.8 – 16.8 months)).

Subgroups: Patients Aged <60 Years vs. Patients Aged ≥60 Years

In the FAS population, the median OS was longer in the subgroup of patients aged <60 years as compared to the subgroup of patients aged ≥60 years (25.4 months (23.8 – 27.9 months) vs. 21.9 months (20.1 – 24.0 months)).

The observation of a longer median OS in the subgroup of patients aged <60 years as compared to the subgroup of patients aged ≥60 years was made in the PAC population (26.7 months (24.5 – 29.7 months) vs. 21.8 months (19.8 – 24.1 months)), whereas in the CAPE population, the median OS was markedly longer in the subgroup of patients aged ≥60 years (22.2 months (19.3 – 29.9 months)) as compared to the subgroup of patients aged <60 years (17.2 months (14.8 – 22.1 months)).

QUALITY OF LIFE – EORTC QLQ-C-30 (PRIMARY OBJECTIVE; TOTAL PAC / CAPE POPULATION AND BY AGE SUBGROUP)

The change in scores (the scale ranges from 0 to a maximum of 100) of global health status / QoL, functional scales and symptom scales / items (EORTC QLQ-C-30) from baseline to week 54 / premature end of bevacizumab (Avastin®) are detailed below for the PAC and CAPE populations. High scores are considered good for global health status and functional scales, while for symptom scales low scores are good.

Total PAC Population

There was only a slight decrease in the score of global health status from baseline to week 54 (n=338; change: -0.37 (95% CI: -3.39 – 2.65); p=0.810), while the score of global health status had decreased markedly from baseline to premature end of bevacizumab (Avastin®) therapy (n=260; change: -5.45 (95% CI: -8.79 – -2.10); p=0.002). The score of nearly all functional scales (physical, role, cognitive, social) had decreased (p<0.05) and the score of all symptom scales / items (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties) had increased (p<0.05) from

baseline to week 54 and/or from baseline to premature end of bevacizumab (Avastin®) therapy.

Subgroups of patients aged <60 years or ≥60 years within the PAC population (global health status)

At baseline, the mean (±STD) score of global health status was slightly higher in the subgroup of patients aged <60 years (51.3 (±23.92)) as compared to the subgroup of patients aged ≥60 years (48.6 (±22.47)), while at week 54 the mean score was slightly higher in the latter subgroup (52.2 (±21.27) vs. 50.4 (±21.08)). For patients with premature end of bevacizumab (Avastin®) therapy, the mean score of global health status had decreased in both subgroups as compared to respective baseline score with a markedly higher mean score in the subgroup of patients aged <60 years (47.0 (±24.17)) as compared to the subgroup of patients aged ≥60 years (42.9 (±22.93)).

Total CAPE Population

The score of global health status had decreased from baseline to week 54 (n=44; change: -2.46 (95% CI: -9.43 – 4.50); *p*=0.480) or from baseline to premature end of bevacizumab (Avastin®) therapy (n=35; change: -9.05 (95% CI: -15.79 – -2.30); *p*=0.010). The score of several functional scales (physical, role, cognitive, social) had decreased (*p*<0.05) and the score of some symptom scales / items (fatigue, pain, constipation, diarrhea) had increased (*p*<0.05) from baseline to week 54 and/or from baseline to premature end of bevacizumab (Avastin®) therapy.

Subgroups of patients aged <60 years or ≥60 years within the CAPE population (global health status)

The mean (±STD) score of global health status at baseline was markedly higher in the subgroup of patients aged <60 years (54.1 (±22.76) as compared to the subgroup of patients aged ≥60 years (47.2 (±23.01)), the mean score of which had increased slightly in both subgroups at week 54 (<60 years: 56.0 (±21.54) vs. ≥60 years: 48.1 (±22.02)) as compared to respective baseline score. For patients with premature end of bevacizumab (Avastin®) therapy, the mean score of global health status had decreased in both subgroups (<60 years: 49.2 (±22.44) vs. ≥60 years: 45.6 (±27.02)) as compared to respective baseline score.

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PATIENT'S EXPERIENCE OF THERAPY SIDE-EFFECTS – INTERFERENCE OF DAILY LIFE OVERALL (TOTAL PAC / CAPE POPULATION AND BY AGE SUBGROUP)

The subjective experience of therapy side-effects was evaluated at the pre-specified timepoints (week 54 / premature end of bevacizumab (Avastin®) therapy) using the patient symptoms questionnaire. Each item evaluated is rated on a 6-point Likert-type scale ranging from "no impairment" to "very strong impairment".

Total PAC Population

At week 54 (358 questionnaires received and evaluated), most patients reported that therapy had interfered with their daily life overall to a certain degree with 16 (4.5%) patients reporting that therapy had impaired their daily life overall very strongly, while only 8 (2.2%) patients reported that therapy had not impaired their daily life overall. For patients with premature end of bevacizumab (Avastin®) therapy (277 questionnaires received and evaluated), a similar pattern was observed with most patients reporting that therapy had interfered with their daily life overall to a certain extent with 24 (8.7%) patients reporting that therapy had impaired their daily life overall very strongly, while only 2 (0.7%) patients reported that therapy had not impaired their daily life overall.

Subgroups of patients aged <60 years or ≥60 years within the PAC population

The proportion of patients having reported that therapy had impaired their daily life overall very strongly was higher in the subgroup of patients aged ≥60 years as compared to the subgroup of patients aged <60 years both at week 54 (n=9; 5.4% vs. n=7; 3.7%) and at premature end of bevacizumab (Avastin®) therapy (n=17; 13.2% vs. n=7; 4.7%).

Total CAPE Population

At week 54 (49 questionnaires received and evaluated), most patients reported that therapy had interfered with their daily life overall to a certain degree, though with no patients reporting that therapy had impaired their daily life overall very strongly. Only 2 (4.1%) patients reported that therapy had not impaired their daily life overall. For patients with premature end of bevacizumab (Avastin®) therapy (38 questionnaires received and evaluated), a similar pattern was observed with most patients reporting that therapy had interfered with their daily life overall to a certain extent with 3 (7.9%) patients reporting

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that therapy had impaired their daily life overall very strongly, while only 1 (2.6%) patient reported that therapy had not impaired their daily life overall.

Subgroups of patients aged <60 years or ≥60 years within the CAPE population

The proportion of patients with premature end of bevacizumab (Avastin®) therapy having reported that therapy had impaired their daily life overall very strongly was higher in the subgroup of patients aged ≥60 years (n=2; 11.8%) as compared to the subgroup of patients aged <60 years (n=1; 4.8%), though with a very low number of observations.

PATIENT'S THERAPY SATISFACTION (TOTAL FAS POPULATION AND BY AGE SUBGROUP)

Patient's overall evaluation of therapy at week 54 or for patients with premature end of bevacizumab (Avastin®) therapy is detailed below for the FAS population, which was assessed by the patient satisfaction questionnaire using a 5-point Likert-type scale (poor, moderate, good, very good, or excellent).

Total FAS Population

Most patients at week 54 found the therapy "good" (n=199; 50.5%) or "very good" (n=89; 22.6%), while only 16 (4.1%) patients found the therapy "excellent" out of the total number of questionnaires received (n=394). Similar proportions of patients were observed for patients with premature end of bevacizumab (Avastin®) therapy having found the therapy "good" (n=99; 32.2%) or "very good" (n=101; 32.9%) out of the total number of questionnaires received (n=307). In total, 54 (17.6%) patients found the therapy "excellent" at premature end of bevacizumab (Avastin®) therapy.

Subgroups of patients aged <60 years or ≥60 years within the FAS population

At week 54, the proportion of patients finding the therapy "good" was identical in the subgroups of patients aged <60 years (n=102; 50.5%) and ≥60 years (n=97; 50.5%), whereas the proportion of patients finding the therapy "very good" was slightly higher in the latter subgroup (n=47; 24.5% vs. n=42; 20.8%). As for patients with premature end of bevacizumab (Avastin®) therapy, the proportion of patients finding the therapy "good" was higher in the subgroup of patients aged <60 years (n=59; 35.5%) as compared to the subgroup of patients aged ≥60 years (n=40; 28.4%), while the proportion of patients

finding the therapy “very good” was markedly higher in the latter subgroup (n=56; 39.7% vs. n=45; 27.1%).

PHYSICIAN’S THERAPY SATISFACTION (FAS POPULATION)

The physicians evaluated the therapy per patient (i.e., on a case-by-case basis). In the FAS population, physicians found the therapy “good” in 989 (47.9%) cases and “very good” in 344 (16.7%) cases. In 60 (2.9%) cases, physicians found the therapy “excellent”. Effectiveness of therapy (n=1897; 91.9%) was the most frequently reported reason for physician’s therapy satisfaction.

SAFETY (FAS / PAC / CAPE POPULATION)

The safety data collected include AEs including AEs of special interest (bevacizumab (Avastin®)-associated hypertension and proteinuria; primary objective) and AEs requiring expedited reporting, SAEs, drug-related (S)AEs, and fatal SAEs (regardless of causality). Fatal events can be either fatal drug-related SAE (assessed as related to bevacizumab (Avastin®) or capecitabine (Xeloda®) treatment) or fatal non-related SAE (assessed as not related to bevacizumab (Avastin®) or capecitabine (Xeloda®)). An AE was considered as a TEAE when assessed as an event having emerged during treatment (on-treatment period), having been absent during the pre-treatment period or worsened relative to the pre-treatment state. Causally related TEAEs in this study were defined as those having a possible, probable or definite relationship to bevacizumab (Avastin®) or capecitabine (Xeloda®) as assessed by respective treating physician.

Prior to November 2017, only bevacizumab (Avastin®) was prepopulated in the corresponding AE-reporting form in the eCRF, while capecitabine (Xeloda®) could only be entered manually on this form (as a possible causal drug). As of November 2017, both bevacizumab (Avastin®) and capecitabine (Xeloda®) were prepopulated in the AE-reporting form in the eCRF. All patients having received capecitabine (Xeloda®) were documented with visits before 1 November 2017 (n=295; 100%), which was the time period in which nearly all documented visits had taken place (n=3052; 99.8%). Six (2.0%) patients were also documented with visits after 1 November 2017, which corresponded to a very small number of visits (n=7; 0.2%). Therefore, statements on causality in this report may only be made with reservations.

(Serious) Treatment-Emergent Adverse Events

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FAS Population

(Serious) Treatment-Emergent Adverse Events

Overall, 1214 (58.8%) patients in the FAS population were reported with a (serious) TEAE where the most frequently (≥5.0% of patients) documented TEAEs (PTs) were hypertension (n=241; 11.7%), fatigue (n=210; 10.2%), polyneuropathy (n=177; 8.6%), nausea (n=145; 7.0%), leukopenia (n=138; 6.7%), diarrhea (n=129; 6.2%) and epistaxis (n=109; 5.3%). Proteinuria was reported in 48 (2.3%) patients.

Serious Treatment-Emergent Adverse Events

Overall, 400 (19.4%) patients in the FAS population were reported with a serious TEAE where the most frequently (≥1.0% of patients) documented TEAEs (PTs) were general physical health deterioration (n=46; 2.2%), death (n=27; 1.3%), pulmonary embolism (n=27; 1.3%), malignant neoplasm progression (n=21; 1.0%) and dyspnea (n=20; 1.0%). Serious hypertension was reported in 16 (0.8%) patients and serious proteinuria in 2 (0.1%) patients.

PAC Population

(Serious) Treatment-Emergent Adverse Events

In total, 1055 (57.9%) patients in the PAC population were reported with a (serious) TEAE where the most frequently (≥5.0% of patients) documented TEAEs (PTs) were hypertension (n=214; 11.8%), fatigue (n=195; 10.7%), polyneuropathy (n=169; 9.3%), leukopenia (n=129; 7.1%), nausea (n=120; 6.6%), epistaxis (n=103; 5.7%), diarrhea (n=101; 5.5%) and alopecia (n=94; 5.2%). Proteinuria was reported in 46 (2.5%) patients.

Serious Treatment-Emergent Adverse Events

In total, 357 (19.6%) patients in the PAC population were reported with a serious TEAE where the most frequently (≥1.0% of patients) documented TEAEs (PTs) were general physical health deterioration (n=41; 2.3%), pulmonary embolism (n=25; 1.4%), death (n=23; 1.3%), malignant neoplasm progression (n=20; 1.1%), dyspnea (n=18; 1.0%) and pyrexia (n=18; 1.0%). Serious hypertension was reported in 14 (0.8%) patients and serious proteinuria in 2 (0.1%) patients.

CAPE Population

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(Serious) Treatment-Emergent Adverse Events

Overall, 195 (66.1%) patients in the CAPE population were reported with a (serious) TEAE where the most frequently (≥5.0% of patients) documented TEAEs (PTs) were palmar-plantar erythrodysaesthesia syndrome (n=68; 23.1%), hypertension (n=36; 12.2%), diarrhea (n=33; 11.2%), nausea (n=29; 9.8%), mucosal inflammation (n=25; 8.5%), fatigue (n=22; 7.5%) and polyneuropathy (n=20; 6.8%). Proteinuria was reported in 2 (0.7%) patients.

Serious Treatment-Emergent Adverse Events

Overall, 58 (19.7%) patients in the CAPE population were reported with a serious TEAE where the most frequently (≥1.0% of patients) documented TEAEs (PTs) were diarrhea (n=7; 2.4%), general physical health deterioration (n=6; 2.0%), death (n=4; 1.4%), pulmonary embolism (n=4; 1.4%), hypertension (n=3; 1.0%) and vomiting (n=3; 1.0%). There were no patients in the CAPE population reported with serious proteinuria.

Treatment-Emergent Adverse Events Causally Related to Bevacizumab (Avastin®)

Hypertension was the most frequently reported bevacizumab (Avastin®)-related TEAE in all analysis populations.

FAS Population

Overall, 625 (30.3%) patients in the FAS population were reported with a TEAE causally related to bevacizumab (Avastin®) where the 10 most frequent TEAEs (PTs) were hypertension (n=177; 8.6%), fatigue (n=84; 4.1%), epistaxis (n=77; 3.7%), polyneuropathy (n=59; 2.9%), nausea (n=52; 2.5%), diarrhea (n=50; 2.4%), leukopenia (n=45; 2.2%), proteinuria (n=38; 1.8%), dyspnea (n=35; 1.7%) and anemia (n=29; 1.4%).

PAC Population

In total, 558 (30.6%) patients in the PAC population were reported with a TEAE causally related to bevacizumab (Avastin®) where the 10 most frequent TEAEs (PTs) were hypertension (n=156; 8.6%), fatigue (n=78; 4.3%), epistaxis (n=74; 4.1%), polyneuropathy (n=56; 3.1%), nausea (n=44; 2.4%), leukopenia (n=42; 2.3%), diarrhea (n=41; 2.3%), proteinuria (n=36; 2.0%), dyspnea (n=31; 1.7%) and anemia (n=28; 1.5%).

CAPE Population

Overall, 92 (31.2%) patients in the CAPE population were reported with a TEAE causally related to bevacizumab (Avastin®) where the 10 most frequent TEAEs (PTs) were hypertension (n=28; 9.5%), fatigue (n=11; 3.7%), palmar-plantar erythrodysaesthesia syndrome (n=10; 3.4%), diarrhea (n=9; 3.1%), nausea (n=9; 3.1%), mucosal inflammation (n=7; 2.4%), polyneuropathy (n=7; 2.4%), epistaxis (n=7; 2.4%), urinary tract infection (n=5; 1.7%), abdominal pain upper (n=4; 1.4%), cough (n=4; 1.4%), dyspnea (n=4; 1.4%) and decreased appetite (n=4; 1.4%).
Proteinuria causally related to bevacizumab (Avastin®) was reported in 2 (0.7%) patients.

Treatment-Emergent Adverse Events Causally Related to Capecitabine (Xeloda®)

Overall, 78 (26.4%) patients in the CAPE population were documented with a TEAE causally related to capecitabine (Xeloda®) where the most commonly (≥1.0% of patients) reported TEAEs (PTs) were palmar-plantar erythrodysaesthesia syndrome (n=48; 16.3%), diarrhea (n=16; 5.4%), nausea (n=10; 3.4%), mucosal inflammation (n=9; 3.1%), vomiting (n=5; 1.7%), fatigue (n=5; 1.7%), polyneuropathy (n=5; 1.7%) and rash (n=4; 1.4%).

Treatment-Emergent Adverse Events Leading to Study Discontinuation

FAS Population

Overall, 76 (3.7%) patients in the FAS population were reported with a TEAE leading to study discontinuation where the most frequently reported TEAEs were polyneuropathy and pulmonary embolism (both n=6; 0.3%), while hypertension (n=4; 0.2%) and proteinuria (n=1; <0.0%) leading to study discontinuation were less frequent.

PAC Population

In total, 61 (3.3%) patients in the PAC population were reported with a TEAE leading to study discontinuation where the most frequently reported TEAE was polyneuropathy (n=6; 0.3%), while hypertension (n=4; 0.2%) and proteinuria (n=1; 0.1%) leading to study discontinuation were less frequent.

CAPE Population

Overall, 16 (5.4%) patients in the CAPE population were reported with a TEAE leading to study discontinuation. The most frequently (≥2 patients) reported TEAEs leading to study

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discontinuation were thrombosis (n=3; 1.0%), diarrhea and palmar-plantar erythrodysaesthesia syndrome (both n=2; 0.7%). There were no patients in the CAPE population reported with hypertension or proteinuria leading to study discontinuation.

Total Number of Death Cases and Fatal Treatment-Emergent Adverse Events

FAS Population

Overall, 988 (47.8%) patients in the FAS population were reported having died during the study.

In total, 111 (5.4%) patients were reported with fatal TEAEs where the most frequently (≥0.2% of patients) reported TEAEs (PTs) were death (n=27; 1.3%), general physical health deterioration (n=23; 1.1%), malignant neoplasm progression (n=14; 0.7%), ascites (n=5; 0.2%), multiple organ dysfunction syndrome (n=5; 0.2%), cardiac failure (n=4; 0.2%), dyspnea (n=4; 0.2%), infection (n=4; 0.2%), metastases to liver (n=4; 0.2%), pleural effusion (n=4; 0.2%) and pulmonary embolism (n=4; 0.2%). There were no patients in the FAS population reported with fatal hypertension or fatal proteinuria.

PAC Population

Overall, 852 (46.8%) patients in the PAC population were reported having died during the study.

In total, 101 (5.5%) patients in the PAC population were reported with fatal TEAEs where the most frequently (≥0.2% of patients) reported TEAEs (PTs) were death (n=23; 1.3%), general physical health deterioration (n=21; 1.2%), malignant neoplasm progression (n=14; 0.8%), ascites (n=5; 0.3%), multiple organ dysfunction syndrome (n=5; 0.3%), cardiac failure (n=4; 0.2%), dyspnea (n=4; 0.2%), infection (n=4; 0.2%), metastases to liver (n=4; 0.2%), pulmonary embolism (n=4; 0.2%), edema (n=3; 0.2%), pleural effusion (n=3; 0.2%), pyrexia (n=3; 0.2%) and vomiting (n=3; 0.2%).

CAPE Population

Overall, 164 (55.6%) patients in the CAPE population were reported having died during the study.

In total, 12 (4.1%) patients in the CAPE population were reported with fatal TEAEs where the most frequently (≥2 patients) reported TEAEs (PTs) were death (n=4; 1.4%) and general physical health deterioration (n=2; 0.7%).

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Fatal Treatment-Emergent Adverse Events Causally Related to Bevacizumab (Avastin®)

FAS Population

In total, 16 (0.8%) patients (31 cases in total) in the FAS population were reported with fatal TEAEs causally related to bevacizumab (Avastin®) including general physical health deterioration (n=4), abdominal pain (n=2), bursitis (n=1), cardiac failure (n=1), cellulitis (n=1), death (n=1), dehydration (n=1), diarrhea (n=1), drug ineffective (n=1), gastrointestinal hemorrhage (n=1), gastrointestinal necrosis (n=1), hemorrhagic anemia (n=1), hypotension (n=1), hypothyroidism (n=1), intestinal ischemia (n=1), large intestinal stenosis (n=1), malignant neoplasm progression (n=1), necrotizing fasciitis (n=1), neutropenia (n=1), osteonecrosis jaw (n=1), pancytopenia (n=1), peritonitis (n=1), pleural effusion (n=1), pulmonary embolism (n=1), septic shock (n=1), and venous thrombosis limb (n=1).

PAC Population

In total, 14 (0.8%) patients (27 cases in total) in the PAC population were reported with fatal TEAEs causally related to bevacizumab (Avastin®) including general physical health deterioration (n=4), abdominal pain (n=2), bursitis (n=1), cardiac failure (n=1), cellulitis (n=1), death (n=1), diarrhea (n=1), drug ineffective (n=1), gastrointestinal hemorrhage (n=1), gastrointestinal necrosis (n=1), hemorrhagic anemia (n=1), intestinal ischemia (n=1), large intestinal stenosis (n=1), malignant neoplasm progression (n=1), necrotizing fasciitis (n=1), neutropenia (n=1), osteonecrosis jaw (n=1), pancytopenia (n=1), peritonitis (n=1), pulmonary embolism (n=1), septic shock (n=1), and venous thrombosis limb (n=1).

CAPE Population

Overall, 2 (0.7%) patients (4 cases in total) in the CAPE population were reported with fatal TEAEs causally related to bevacizumab (Avastin®) including dehydration, hypotension, hypothyroidism and pleural effusion.

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Treatment-Emergent Adverse Events of Special Interest – Primary Objective (Total FAS Population, by Age Subgroup and by Dose Intensity of Bevacizumab (Avastin®))

Hypertension reported as a TEAE

In total, 109 (15.4%) patients with pre-existing hypertension and 132 (9.7%) without pre-existing hypertension were reported with hypertension documented as a TEAE. In the subgroups of patients aged <60 years or ≥60 years, no major differences in the proportions of patients with hypertension reported as a TEAE were observed between the age subgroups with (<60 years: n=36; 15.9% vs. ≥60 years: n=73; 15.2%) or without (<60 years: n=77; 9.4% vs. ≥60 years: n=55; 10.2%) pre-existing hypertension. Regarding the subgroups of patients with a different dose intensity of bevacizumab (Avastin®) (<2.5 mg/kg per week, ≥ 2.5 to < 5 mg/kg per week or ≥5 mg/kg per week), for patients with pre-existing hypertension and a bevacizumab (Avastin®) dose of ≥5 mg/kg per week, 17 (13.5%) patients were reported with hypertension as a TEAE, which was a lower relative frequency as compared to the subgroups of patients with a dose intensity of bevacizumab (Avastin®) of <2.5 mg/kg per week (n=3; 16.7%) or ≥ 2.5 to < 5 mg/kg per week (n=88; 16.1%). With regards to patients without pre-existing hypertension and a bevacizumab (Avastin®) dose of ≥5 mg/kg per week, 19 (7.1%) patients were reported with hypertension as a TEAE, which was a lower relative frequency as compared to the subgroup of patients with a bevacizumab (Avastin®) dose of ≥ 2.5 to < 5 mg/kg per week (n=111; 10.8%), while no patients in the subgroup of patients with a bevacizumab (Avastin®) dose of <2.5 mg/kg per week were reported with hypertension as a TEAE. Of note, the subgroup of patients with a bevacizumab (Avastin®) dose of <2.5 mg/kg per week (with / without pre-existing hypertension) was rather small (N=18 / N=24), whereby a single patient changes the percentage notably.

Most patients were documented with hypertension of CTCAE grade 1 or 2 both in the subgroups of patients with (CTCAE grade 1: n=37; 5.2%; CTCAE grade 2: n=53; 7.5%) and without (CTCAE grade 1: n=55; 4.1%; CTCAE grade 2: n=69; 5.1%) pre-existing hypertension. Hypertension of CTCAE grade 4 was only reported in the subgroup of patients with pre-existing hypertension (n=3; 0.4%). No patients were reported with fatal hypertension.

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For most patients with hypertension reported as a TEAE, no action had been taken with regards to bevacizumab (Avastin®) therapy both in the subgroups of patients with (n=78; 11.0%) and without (n=92; 6.8%) pre-existing hypertension.

Proteinuria reported as a TEAE

In total, 48 (2.3%) patients were reported with proteinuria documented as a TEAE. Similar proportions of patients in the subgroups of patients aged <60 years (n=27; 2.6%) and patients aged ≥60 years (n=21; 2.1%) were reported with proteinuria as a TEAE. Regarding the subgroups of patients with different dose intensity of bevacizumab (Avastin®) (<2.5 mg/kg per week, ≥ 2.5 to < 5 mg/kg per week or ≥5 mg/kg per week), the highest proportion of patients reported with proteinuria documented as a TEAE was observed in the subgroup of patients with a dose intensity of bevacizumab (Avastin®) of <2.5 mg/kg per week (n=3; 7.1%) as compared to the subgroup of patients with a dose intensity of bevacizumab (Avastin®) of ≥ 2.5 to < 5 mg/kg per week (n=38; 2.4%) or ≥5 mg/kg per week (n=5; 1.3%). Noteworthy, the subgroup of patients with a bevacizumab (Avastin®) dose of <2.5 mg/kg per week was rather small (N=42), whereby a single patient changes the percentage notably.

Most patients were documented with proteinuria of CTCAE grade 1 (n=16; 0.8%) or 2 (n=28; 1.4%). None of the patients with proteinuria reported as a TEAE were documented with proteinuria of CTCAE grade 4 or grade 5.

For 21 (43.8%) of the 48 patients with proteinuria reported as a TEAE, no action had been taken with regards to bevacizumab (Avastin®) therapy.

Conclusions

First-line therapy with bevacizumab (Avastin®) in combination with paclitaxel or capecitabine (Xeloda®) is effective in routine clinical practice in patients with HER2-negative advanced, recurrent or metastatic breast cancer. The ORR and median PFS observed in this study are comparable to the results reported in the pivotal studies.

The effectiveness outcome (ORR, PFS, OS) was better in patients treated with the combination partner paclitaxel as compared to the combination partner capecitabine (Xeloda®) as well as in younger (<60 years), hormone receptor-positive, HER2-negative, or hypertensive (at baseline) patients, bearing in mind the differences in patient

characteristics and the overlap between the analysis populations. Particularly noteworthy is that the effectiveness in TNBC patients compared to hormone receptor-positive, HER2-negative patients is in line with results reported in randomized, controlled clinical studies.

A direct comparison of the effectiveness in this study with results obtained in randomized, controlled clinical studies is subject to limitations due to differences in patient characteristics and study settings including clear cut inclusion and exclusion criteria, assessment schemes and assessment specifications as well as the high number of censored patients in this study, especially patients censored at early timepoints.

The tumor board was the main deciding party and “efficacy of therapy” and “guideline” were the main selection criteria for choice of therapy across all analysis populations.

While most patients (low number of questionnaires) and physicians were satisfied with bevacizumab (Avastin®) therapy in combination with paclitaxel or capecitabine (Xeloda®) with effectiveness being the most common reason for physician’s satisfaction, the QoL was impaired for most patients during therapy, particularly patients with premature end of bevacizumab (Avastin®) therapy and with capecitabine (Xeloda®) as combination partner.

Bevacizumab (Avastin®) plus either paclitaxel or capecitabine (Xeloda®) combination therapy is well tolerated. The safety information reported in this study is consistent with the known safety profile of bevacizumab (Avastin®).